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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,653	03/29/2004	Michal Eisenbach-Schwartz	EIS-SCHWARTZ=2B	9591

1444 7590 04/16/2007

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,653	EISENBACH-SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-13 and 17-51* is/are pending in the application.

4a) Of the above claim(s) *21,26-30,35 and 40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/30/04; 10/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 25 October 2006 and 02 March 2006 have been entered in full. Claims 6, 8, 14, and 16 are cancelled. Claims 18-51 are added. Claims 1-3, 7, 9-11, and 50-51 are amended.

Election/Restrictions

1. This application contains claims directed to the following patentably distinct species: NS-specific antigen:

a. myelin basic protein

b. myelin oligodendrocyte glycoprotein

c. proteolipid protein

d. myelin-associated glycoprotein

e. S-100

f. β-amyloid

g. Thy-1

h. P0

i. P2

j. a neurotransmitter receptor

k. Nogo-A

l. Nogo-B

m. Nogo-C

n. Nogo receptor

The species are independent or distinct because each of the antigens listed as (a)-(n) have different structural and functional characteristics. The species are independent or distinct because each requires separate, non-coextensive searches. For example, a technical literature search for administration of myelin basic protein may not result in relevant art with respect to administration of P2.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-3, 9, and 19 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

2. During a telephone conversation with Roger Browdy on 22 November 2006 a provisional election was made with traverse to prosecute the species of myelin basic protein (MBP). Affirmation of this election must be made by applicant in replying to this Office action. Claims 21, 26-30, 35, and 40-44 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51 are under consideration in the instant application.

Specification

3. The abstract of the disclosure is objected to because the legal term "said" is used. Applicant is reminded of the proper language and format for an abstract of the disclosure. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 1 12:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **(I)** a method for reducing secondary neuronal degeneration or a method for ameliorating the secondary neurodegenerative effects that follow neuronal damage caused by an injury, disease, disorder or condition in the CNS or PNS comprising administering to an individual myelin basic protein (MBP), p51-70 of MBP, or T cells activated against MBP or p51-70, thereby reducing secondary neuronal degeneration at the injury site, *does not reasonably provide enablement for* a method

for reducing secondary neuronal degeneration in the CNS or PNS comprising administering to an individual an effective amount of (i) an NS-specific antigen that is not an autoimmune antigen of that disease, (ii) an immunogenic or cryptic epitope thereof, or (iii) a modification of (i) that is immunogenic and maintains at least 90% identity with (i), in such a manner that T cells become activated against the NS-specific antigen or administering an effective amount of T cells that are activated against said NS-specific antigen, said immunogenic or cryptic epitope thereof, or said modification thereof.

The specification is also enabling for **(II)** a method for reducing secondary neuronal degeneration or a method for ameliorating the secondary neurodegenerative effects that follow neuronal damage caused by an injury in the CNS or PNS comprising administering to an individual NogoA p472 (SEQ ID NO: 19) peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for reducing secondary neuronal degeneration in the CNS or PNS comprising administering to an individual an effective amount of (i) an NS-specific antigen that is not an autoimmune antigen of that disease, (ii) an immunogenic or cryptic epitope thereof, or (iii) a modification of (i) that is immunogenic and maintains at least 90% identity with (i), in such a manner that T cells become activated against the NS-specific antigen or administering an effective amount of T cells that are activated against said NS-specific antigen, said immunogenic or cryptic epitope thereof, or said modification thereof.

The specification of the instant application discloses that rats injected with anti-MBP activated T cells after optic nerve injury had significantly greater numbers retinal ganglion cells

in the retinas as compared to control rats (page 68). The specification teaches that only the MBP-specific autoimmune T cells has a substantial effect in limiting the extent of secondary degeneration (page 69, lines 1-9). The specification teaches that immunization of Lewis rats after spinal cord contusion with anti-MBP T cells results in earlier recovery from spinal shock (bottom of page 76) and better locomotor recovery as compared to untreated injured rats (pages 77-78). The specification discloses that retrograde labeling of the descending spinal tracts indicates that the reduction in injury-induced functional deficit observed in T cell-treated rats can be attributed to the sparing of spinal tracts, results in a higher degree of neuron viability (page 79, lines 16-20). Furthermore, the specification discloses that immunization of Sprague-Dawley rats after spinal cord contusion with Nogo p472 peptide results in significantly improved overall functional recovery compared to control rats injected with PBS of CFA (bottom of page 93 through pg 94).

However, the specification does not teach the reduction or inhibition of secondary neuronal degeneration by administration of any nervous system-specific antigens, other than Nogo p472, myelin basic protein (MBP), p51-70 of MBP, or T cells activated against MBP or p51-70. The specification also does not teach that all possible peptides derived from all possible NS-specific antigens (or activated T cells thereto) are able to reduce secondary neuronal degeneration in the central nervous system or peripheral nervous system of an individual. Undue experimentation would be required of the skilled artisan to generate peptides to all possible NS-specific antigens (and activated T cells thereto) and administer each of these peptides (or cells) to an individual to achieve the desired result of reducing secondary neuronal degeneration. Since the specification also provides no guidance regarding what immunogenic/cryptic epitopes or

modified NS-specific antigens that are at least 90% identical to the NS-specific antigen should be utilized for the desired activity, the skilled artisan must resort to trial and error experimentation to determine which peptides might yield one with the desired activity. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". Relevant literature even teaches that certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). For example, the Examiner has interpreted the administration of Nogo-A p472 (SEQ ID NO: 19) to be a critical feature of the claimed method since relevant literature teaches that other Nogo-A derived peptides possess growth-cone-collapsing activity and inhibit neurite outgrowth (for example, GrandPre et al. Nature 403: 439-444, 2000; see pg 442, Figures 4-5). Additionally, even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is

dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The Applicant's list of NS-specific antigens in the specification is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Relevant literature also teaches that about 200,000 distinct mRNA sequences are thought to be expressed in the brain alone (a component of the central nervous system) and that this diversity results from the greater number and variety of cell types in the brain as compared to cells in the more homogeneous body tissues (pg 49, ¶ 1; Schwartz, J., "Synthesis and Trafficking of Neuronal Proteins", Principles of Neural Science, Connecticut: Appleton and Lange, 1991, pages 49-65). Schwartz states that the three membrane systems which constitute separate compartments within the neuron are made up of different proteins and serve separate functions within the cell (pg 50). Schwartz also continues to explain that a nerve cell makes three general classes of proteins: cystolic, nuclear/mitochondrial/peroxisomal, and cell membrane/secretory (pg 50-55). Post-filing date literature also reiterates that the central nervous system alone expresses a large and divergent proteome, comprising thousands of unique proteins (see for example, Yu et al., Molec Cellul Proteomics 3: 896-907, 2004). Therefore, due

to the large quantity of proteins/antigens present in the central nervous system alone, the present invention is unpredictable and complex wherein one skilled in the art may not necessarily reduce or inhibit secondary neuronal degeneration in the central nervous system or peripheral nervous system comprising administering (1) all types of NS-specific peptides, immunogenic or cryptic epitopes thereof, or an antigen that is 90% identical to said NS-specific antigen or (2) T cells activated against said NS-specific antigen, immunogenic or cryptic epitope thereof, or said modification thereof.

Due to the large quantity of experimentation necessary to identify all possible NS-specific antigens, immunogenic or cryptic epitopes thereof, or antigens that are 90% identical to said NS-specific antigen (or activated T cells thereto) and then reduce secondary neuronal degeneration by administration of any of the above; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of the effects of administering any NS-specific antigen or NS-specific T cells to an individual, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

4. Claims 1-5, 7, 9-13, 15, 17, 18, 22, 23, 31, 36, 37, 45-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for reducing secondary neuronal degeneration in the CNS or PNS comprising administering to an individual an effective amount of (i) an NS-specific antigen that is not an autoimmune antigen of that disease, (ii) an immunogenic or cryptic epitope thereof, or (iii) a modification of (i) that is immunogenic and maintains at least 90% identity with (i), in such a manner that T cells become activated against the NS-specific antigen or administering an effective amount of T cells that are activated against said NS-specific antigen, said immunogenic or cryptic epitope thereof, or said modification thereof.

The specification of the instant application discloses that rats injected with anti-MBP activated T cells after optic nerve injury had significantly greater numbers retinal ganglion cells in the retinas as compared to control rats (page 68). The specification teaches that immunization of Lewis rats after spinal cord contusion with anti-MBP T cells results in earlier recovery from spinal shock (bottom of page 76) and better locomotor recovery as compared to untreated injured rats (pages 77-78). Furthermore, the specification discloses that immunization of Sprague-Dawley rats after spinal cord contusion with Nogo p472 peptide results in significantly improved overall functional recovery compared to control rats injected with PBS of CFA (bottom of page 93 through pg 94). The specification teaches that the term "NS-specific antigen" refers to "an antigen of the NS that specifically activates T cells such that following activation the activated T cells accumulate at a site of injury or disease in the NS of the patient. Examples of NS-specific antigens according to the invention include, but are not limited to, myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), myelin-associated glycoprotein (MAG), S-100, β-amyloid, Thy-l, P0, P2, neurotransmitter receptors, the protein Nogo (Nogo-A, Nogo-B and Nogo-C) and the Nogo receptor (NgR)" (page 9, [0024]). The

specification further discloses that "also encompassed by the present invention are analogs of NS-specific antigens including, but not being limited to, those molecules comprising regions that are substantially homologous to the full-length NS-specific antigen, or fragments thereof. In various embodiments, these analogs will have at least 60% or 70% or 80% or 90% or 95% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art or whose encoding nucleic acid is capable of hybridizing to a coding nucleotide sequence of the full-length NS-specific antigen, under high stringency, moderate stringency, or low stringency conditions" (page 41, [0100]).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the NS-specific antigens, an immunogenic or cryptic thereof, or a modification of the antigen that maintains at least 90% identity with the NS-specific antigen (or T cells activated against all of the above) of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The NS-specific antigen itself is required. See *Fiers v. Revel*, 25

USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only methods of utilizing a specific NS-specific antigen or a specific immunogenic or cryptic epitope of the antigen (or activated T cells thereto), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-5, 7, 9-13, 15, 17-20, 22-25, 31-34, 36-39, and 45-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 14-22 of copending Application No. 11/563,630. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite a method for reducing secondary neuronal degeneration in the central or peripheral nervous system comprising administering a modified nervous system peptide antigen or administering an effective amount of T cells that are activated against said modified peptide. The instant claims recite that the modified nervous system specific antigen is immunogenic and maintains at least 90% identity with the NS-specific antigen. The claims of the '630 application recite that the modification of the self-peptide derived from a CNS antigen consists in the replacement of one or more amino acid residues of the self-peptide by different amino acid residues. Both sets of claims also recite that NS or CNS specific antigen is selected from the group consisting of myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), myelin-associated glycoprotein (MAG), S-100, β-amyloid, Thy-l, P0, P2, and a neurotransmitter receptor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
30 March 2007

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER